552,892

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
21 October 2004 (21.10.2004)

PCT

(10) International Publication Number
WO 2004/089349 A2

(51) International Patent Classification[7]: A61K 31/00, 31/4164, 31/4178, A61P 25/08

(21) International Application Number: PCT/FI2004/000220

(22) International Filing Date: 8 April 2004 (08.04.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/461,413 10 April 2003 (10.04.2003) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2004/089349 A2

(54) Title: TREATMENT OF EPILEPSY

(57) Abstract: The disclosure relates to a method for the inhibition of the development of epilepsy with an alpha2-adrenoceptor antagonist or a pharmaceutically acceptable salt or ester thereof.

TREATMENT OF EPILEPSY

FIELD OF THE INVENTION

The present invention relates to a method for inhibiting the development of epilepsy. One embodiment of the present invention relates, for instance, to a method for the inhibition of the development of epilepsy with an alpha2-adrenoceptor antagonist.

BACKGROUND OF THE INVENTION

Symptomatic partial epilepsy often develops in 3 phases: an initial brain damaging insult like status epilepticus (SE), head trauma, stroke, infection, neurosurgical operation ⇨ latency phase (epileptogenesis) ⇨ spontaneous seizures (epilepsy). The current treatment of epilepsy exclusively focuses on prevention or suppression of seizures. Thus, there is an unmet need for a pharmaceutical capable of inhibiting the development of epilepsy in the patients at risk. Further, if epilepsy can not be completely prevented, it would be beneficial to modify the disease process in such a way that epileptogenesis leads to a milder and easier-to-control disease.

Previous studies have convincingly demonstrated that α2-adrenergic agonists are anticonvulsant in acute seizure models, including chemically induced seizures with kainic acid (Baran H. et al., Eur J Pharmacol 1985:113:263-269) or pentylenetetrazol (Kulkarni SK., Arch Int Pharmacodyn 1981:252:124-132) as well as audiogenic seizures in genetically epilepsy prone DBA/2J mice (Kellog C., J Neurochem 1976:106:87-103). On the other hand, studies with nonspecific α2-adrenoceptor antagonists show that they are proconvulsants in rats (Gellmann RL. et al., J Pharmacol Exp Ther 1987:241(3):891-898, Janumpalli S. et al., J Neurosci 1998:18(6):2004-2008). In humans, oral administration of an α2-adrenoceptor antagonist, yohimbine, increased cortical excitability induced by transcranial magnetic stimulation (Plewnia C et al., Neurosci Lett 2001:307:41-44).

Atipamezole is a specific alpha2- adrenoceptor antagonist that has a high alpha2/alpha1- selectivity ratio and does not display a species differences (human and

rodent) in its effects. Like other α2-adrenoceptor antagonists, acute administration of atipamezole has a proconvulsant effect of kainate-induced seizures (Halonen T. et al., Brain Res 1995:693:217-224).

DETAILED DESCRIPTION OF THE INVENTION

Applicants have surprisingly discovered that a selective alpha2-adrenoceptor antagonist, atipamezole (4-(2-ethyl-2,3-dihydro-1H-inden-2-yl)-1H-imidazole hydrochloride), has a clear disease-modifying effect on epileptogenesis, that is, epilepsy that develops is milder and can be non-progressive. Thus, selective alpha2-adrenoceptor antagonists, such as atipamezole, and their pharmacologically acceptable esters or salts, can be used for the inhibition of the development of epilepsy.

Alpha2-adrenoceptor antagonists of the invention include, without limitation, atipamezole, idazoxan, efaroxan, and their analogs and pharmaceutically acceptable salts and esters. 4-(2-ethyl-2,3-dihydro-1H-inden-2-yl)-1H-imidazole, known as atipamezole, and its pharmaceutically acceptable acid addition salts with inorganic and organic acids generally used for the purpose, are described in U.S. Patent. No. 4,689,339, which is incorporated herein by reference. The halogenated analogs of atipamezole, for example 4-(2-ethyl-5-fluoro-2,3-dihydro-1H-inden-2-yl)-1H-imidazole and 4-(2-ethyl-5,6-difluoro-2,3-dihydro-1H-inden-2-yl)-1H-imidazole and their pharmaceutically acceptable acid addition salts have been described in U.S. Patent No. 5,498,623, which is incorporated herein by reference. Efaroxan, 2-(2-ethyl- 2,3-dihydro-2-benzofuranyl)-4,5-dihydro-1H-imidazole, and its pharmaceutically acceptable acid addition salts, are described in U.S. Patent 4,411,908, which is incorporated herein by reference.

For the purposes of this disclosure the term "selective alpha2-adrenoceptor antagonist" refers to a compound having an alpha2/alpha1 ratio greater than about 30.

The precise amount of the drug to be administered to a mammal according to the present invention is dependent on numerous factors known to one skilled in the art, such as the compound to be administered, the general condition of the patient, the condition to be treated, the desired duration of use, the type of mammal, the method and route of administration, etc. For example, for atipamezole, the usual daily dosage can be from 1 to

50 mg for a 70 kg person, and can be from 10 to 30 mg, for instance, divided in 1 to 4 individual doses. In another embodiment, the dose for atipamezole can be about 10 mg. Typical routes of administration include, without limitation, oral, transdermal, transmucosal, and parenteral routes.

The use of the alpha2-adrenoceptor antagonist can be started, for example, one or more days after an initial brain damaging insult like head trauma, brain ischemia, infection or neurosurgical operation, and it can be started even several weeks after such insult. Furthermore, it can be started during the interictal period (i.e. a period between two seizures) following the initial brain damaging insult. Depending on the severity of the initial brain damaging insult and the general condition of the patient, the treatment can be continued for from several weeks to several months and even years.

The invention will be further illustrated by the following example, which is intended to be purely exemplary of the invention, and should not be construed as limiting.

EXAMPLE 1

To mimic the clinical environment, α2-adrenoceptor antagonist treatment with atipamezole was started 1 wk after induction of status epilepticus (SE) with subcutaneous Alzet minipumps and continued for 9 wk. Two independent studies were carried out.

Animals

Male Harlan Sprague-Dawley rats (300-350 g; Netherlands) were used in this study. After implantation of electrodes, rats were housed in individual cages at a temperature of 19-21 °C, with humidity at 50-60% and lights on 7.00-19.00. Standard food pellets and water were freely available.

Implantation of electrodes

The animals were anaesthetized with an intraperitoneal injection of sodium pentobarbital (60 mg/kg) and chloral hydrate (60 mg/kg) and inserted into a stereotaxic frame (lambda and bregma at the same horizontal level). A pair of stimulating electrodes (0.5 mm tip separation) was implanted into the lateral nucleus of the left amygdala (3.6

mm posterior, 5.0 mm lateral, and 6.5 mm ventral to bregma). One stainless steel screw was inserted into the skull above the right frontal cortex and served as cortical electrode (3 mm anterior to the bregma, 2 mm lateral to midline). Two stainless steel screws were inserted into the skull bilaterally over the cerebellum, which served as indifferent and ground electrodes. The electrodes were fixed with dental acrylate. The rats were allowed to recover from surgical operation for 14 d, after which electrical stimulation was initiated.

Induction of SE

After discharge threshold was assessed by stimulating the amygdala with a one-second train of one-msec bipolar square-wave pulses (60 Hz, 50-400 μA peak to peak). Only those rats in which after discharges could be induced at 400 μA or at lower current level were included in the study.

To induce SE, the amygdala was stimulated repeatedly at 500 msec intervals with a train of pulses lasting 100 msec (1 msec 60 Hz bipolar pulses at 400 μA peak to peak). After 20 minutes, stimulation was interrupted, and the behavioral and electrographic seizure activity was observed for 5 min. If the animal did not meet the criterion of clonic SE (continuous epileptiform spiking and recurrent clonic seizures), stimulation was resumed and the behavior of the animal was checked again after 10 min. Once the criterion of SE was achieved, no further stimulation was given. After 3 h, SE was terminated by injecting diazepam 20 mg/kg (i.p.).

Administration of vehicle, diazepam, and atipamezole

Vehicle (0.9% saline, Natrosteril 9mg/ml, Baxter, Vantaa, Finland) was administered via subcutaneous Alzet minipumps with a pumping rate of 9.15 μl/h in 1-wk and 2.61 μl/h in 8-wk pumps starting 1 wk after stimulation. Minipumps were implanted subcutaneously to the back between the scapulae according to the instructions provided by manufacturer. For implantation, animals were anesthetized with an intraperitoneal injection of sodium pentobarbital (60 mg/kg) and chloral hydrate (60 mg/kg).

Diazepam was administered at 3 h after the beginning of SE (20 mg/kg, i.p.). Atipamezole treatment was started 1 wk after SE. Compound was administered with subcutaneous Alzet osmotic minipumps and continued for 9 wk. Atipamezole was

dissolved into sterile 0.9 % NaCl. The concentration of atipamezole was adjusted according to the weight of the rat and pumping rate to obtain a constant flow-rate of 100µg/kg/h.

Study Groups

Treatment groups in Study 1:

- DZP (diazepam) + vehicle (n=11): Rats with SE treated with DZP (20 mg/kg, i.p.) at 3 h after the beginning of SE. Chronic treatment with vehicle (0.9% NaCl, subcutaneous Alzet minipumps) for 9 wk starting 1 wk after SE.
- DZP+ atipamezole (n=7): Rats with SE treated with DZP (20 mg/kg, i.p.) at 3 h after the beginning of SE. Chronic treatment with atipamezole (100µg/kg/h, subcutaneous Alzet minipumps) for 9 wk starting 1 wk after SE.

Treatment groups in Study 2:

- Controls (n=9): Operated, non-stimulated and non-treated controls.
- Ø + vehicle (n=11): No treatment at 3 h after the beginning of SE. Chronic treatment with vehicle (0.9% NaCl in subcutaneous Alzet minipump) for 9 wk starting 1 wk after SE.
- DZP + vehicle (n=10): Diazepam treatment (20 mg/kg, i.p.) at 3 h after the beginning of SE. Chronic treatment with vehicle (0.9% NaCl in subcutaneous Alzet minipump) for 9 wk starting 1 wk after SE.
- Ø + atipamezole (n=10). No treatment at 3 h after the beginning of SE. Chronic treatment with atipamezole (100µg/kg/h, subcutaneous Alzet minipumps) for 9 wk starting 1 wk after SE.
- DZP + atipamezole (n=12). Diazepam treatment (20 mg/kg, i.p.) at 3 h after the beginning of SE. Chronic treatment with atipamezole (100µg/kg/h, subcutaneous Alzet minipumps) for 9 wk starting 1 wk after SE.

RESULTS

The data combined from the two different studies is summarized in Table 1. None of the animals in the DZP+atipamezole group developed severe epilepsy, whereas 50% the rats in the DZP+vehicle group had >1 seizure/day ($p>0.05$). No progression was observed between the two follow-ups.

Table 1. Number of animals with severe (>1 seizure/day) or mild (≤1 seizure/day) epilepsy in the different treatment groups.

	During treatment		**After treatment**		**All**	
	severe	mild	severe	mild	severe	mild
Study 1						
DZP + vehicle	4/10	6/10	4/9	5/9	5/10	5/10
DZP + atipamezole	0/3	3/3	0/4	4/4	0/5	5/5
Fischer's exact test	ns		ns		ns	
Study 2						
Ø + vehicle	3/8	5/8	3/7	4/7	4/8	4/8
DZP + vehicle	3/4	1/4	2/3	1/3	2/4	2/4

Ø + atipamezole	1/8	7/8	1/7	6/7	1/8	7/8
DZP + atipamezole	0/9*	9/9	0/9*	9/9	0/9	9/9#
Fischer's exact test	p<0.05		p<0.05		p<0.05	
Study 1 + Study 2						
Ø/DZP + vehicle	10/22	12/22	10/19	9/19	11/22	11/22
Ø/DZP + atipamezole	1/20	19/20	1/20	19/20	1/22	21/22
Fischer's exact test	p<0.01		p<0.01		p<0.01	

Abbreviations: ns, nonsignificant. Statistical significances between the atipamezole treated and untreated animals: * p<0.05 compared to the DZP+vehicle group; # p<0.05 compared to the Ø+vehicle group (Fischer's exact test)

We claim:

1. Use of an alpha2-adrenoceptor antagonist in the manufacture of a medicament for inhibiting the development of epilepsy in a patient at risk of developing epilepsy.

2. The use according to claim 1, wherein the alpha2-adrenoceptor antagonist is atipamezole or a pharmaceutically acceptable salt thereof.

3. The use according to claim 1, wherein the alpha2-adrenoceptor antagonist is idazoxan or a pharmaceutically acceptable salt thereof.

4. The use according to claim 1, wherein the alpha2-adrenoceptor antagonist is efaroxan or a pharmaceutically acceptable salt thereof.

5. The use according to claim 1, wherein the alpha2-adrenoceptor antagonist is 4-(2-ethyl-5-fluoro-2,3-dihydro-1H-inden-2-yl)-1H-imidazole or a pharmaceutically acceptable salt thereof.

6. The use according to claim 1, wherein the alpha2-adrenoceptor antagonist is an analog chosen from analogs of atipamezole, analogs of idazoxan, and analogs of efaroxan.

7. The use according to claim 1, wherein said risk of developing epilepsy is caused by head trauma, brain ischemia, infection or neurosurgical operation.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
21 October 2004 (21.10.2004)

PCT

(10) International Publication Number
WO 2004/089349 A3

(51) International Patent Classification[7]: A61K 31/00, 31/4164, 31/4178, A61P 25/08

(21) International Application Number: PCT/FI2004/000220

(22) International Filing Date: 8 April 2004 (08.04.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/461,413 10 April 2003 (10.04.2003) US

(71) Applicant *(for all designated States except US)*: **ORION CORPORATION** [FI/FI]; Orionintie 1, FI-02200 Espoo (FI).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **HAAPALINNA, Antti** [FI/FI]; Markulantie 8, FI-20360 Turku (FI). **PITKÄNEN, Asla** [FI/FI]; Hauenkoukku 18 as. 2, FI-70700 Kuopio (FI).

(74) Agent: **ORION CORPORATION**; ORION PHARMA, Legal Affairs and Intellectual Property Rights, P.O.Box 65, FI-02101 Espoo (FI).

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(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report: 9 December 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: USE OF AN ALPHA2-ADRENOCEPTOR ANTAGONIST FOR THE TREATMENT OF EPILEPSY

(57) Abstract: The disclosure relates to a method for the inhibition of the development of epilepsy with an alpha2-adrenoceptor antagonist or a pharmaceutically acceptable salt or ester thereof.

WO 2004/089349 A3

INTERNATIONAL SEARCH REPORT

International Application No
PCT/FI2004/000220

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/00 A61K31/4164 A61K31/4178 A61P25/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BIOSIS, SCISEARCH, CHEM ABS Data, MEDLINE, EMBASE, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	PITKANEN ASLA ET AL: "Atipamezole, an alpha2-adrenoceptor antagonist, has disease-modifying effects on epileptogenesis in rats." EPILEPSIA, vol. 44, no. Supplement 9, 2003, pages 261-262, XP001193760 & ANNUAL MEETING OF THE AMERICAN EPILEPSY SOCIETY; BOSTON, MA, USA; DECEMBER 05-10, 2003 ISSN: 0013-9580 the whole document	1,2,7
P,X	WO 03/082825 A (SIRVIOE JOUNI ; ORION CORP (FI); SALLINEN JUKKA (FI)) 9 October 2003 (2003-10-09) abstract page 5, line 12 - line 22; claims 1,9	1,7

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 June 2004	30. 09. 2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2, NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hoff, P

INTERNATIONAL SEARCH REPORT

International Application No
PCT/FI2004/000220

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PITKANEN A (REPRINT) ET AL: "Disease modifying effects of alpha2-adrenoceptor blocker, atipamezole , on epileptogenesis in rats" EPILEPSIA, (FEB 2003) VOL. 44, SUPP. [8], PP. 175-175. PUBLISHER: BLACKWELL PUBLISHING INC, 350 MAIN ST, MALDEN, MA 02148 USA. ISSN: 0013-9580., February 2003 (2003-02), XP008031700 the whole document	1,2,7
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/FI2004/000220

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1, 7 (all partially), 2

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1(partially),2,7(partially)

   Use of an alpha2-adrenoceptor antagonist which is atipamezole for inhibiting the development of epilepsy

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2. claims: 1(partially),3,6-7(partially)

   Use of an alpha2-adrenoceptor antagonist which is idazoxan or an analog thereof for inhibiting the development of epilepsy

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3. claims: 1(partially),4,6-7(partially)

   Use of an alpha2-adrenoceptor antagonist which is efaroxan or an analog thereof for inhibiting the development of epilepsy

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4. claims: 1(partially),5,6-7(partially)

   Use of an alpha2-adrenoceptor antagonist which is an analog of atipamezole (e.g. 4-(2-ethyl-5-fluoro-2,3-dihydro-1H-inden-2-yl)-1H-imidazole) for inhibiting the development of epilepsy

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/FI2004/000220

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